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Claimpto

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--Claim 1. (Currently amended) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) pre-sterilizing all composition ingredients;

[[a]] b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

[[b]] c) mixing and emulsifying said first emulsion and a second aqueous phase ~~in a mixer with an energy input~~ to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

[[c]] d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles ~~of pre-determined size relative to energy input~~ of pre-determined, uniform size distribution; and

[[d]] e) ~~filtering~~ adjusting the concentration of the multivesicular liposomal particle composition by cross-flow filtration,

wherein all steps are carried out under aseptic conditions~~, and wherein all solutions are sterile filtered prior to use, and wherein the multivesicular liposomal particle composition is immediately suitable for administration into humans~~.

Claim 2. (Currently amended) The process of claim 1, wherein at least one mixing step is carried out in a dynamic or static mixer.--

3. The process of claim 2, wherein the static mixer is of Kenics or Koch design.

4. The process of claim 3, wherein the first emulsion and second aqueous solution are passed through the mixer at a linear velocity of from about 100 cm/min to about 500 cm/min.

5. The process of claim 1, wherein the volume ratio of the first aqueous phase to the water-immiscible solvent phase is from about 0.33 to about 1.6.

6. The process of claim 1, wherein the volume ratio of the first emulsion to the second aqueous phase is from about 0.05 to about 0.5.

7. The process of claim 1, wherein the at least one amphipathic lipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, sphingomyelins, lysophosphatidylcholines, lysophosphatidylethanolamines, are phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, phosphatidic acids, cardiolipins, acyl trimethylammonium propane, diacyl dimethylammonium propane, stearylamine, and ethyl phosphatidylcholine.

8. The process of claim 1, wherein the at least one neutral lipid is selected from the group consisting of glycerol esters, glycol esters, tocopherol esters, sterol esters, alkanes and squalenes.

9. The process of claim 1, wherein the second aqueous phase further comprises at least one sugar.

10. The process of claim 1, wherein the second aqueous phase further comprises at least one amino acid.

claim 11 cancelled

12. The process of claim 11, wherein the ~~primary filtration~~ filtering comprises:

a) a first concentration of the multivesicular liposomal particle composition, resulting in a concentration increase of from 2-6 times; and

b) a buffer exchange, resulting in a pH of the multivesicular liposomal particle composition of between about 5 and about 8.

13. The process of claim 12, further comprising a second concentration step.

14. (Amended) The process of claim [11] 12 wherein the [primary filtration] filtering is carried out [by cross flow filtration] with a hollow fiber filter.

15. The process of claim 14, wherein the ~~primary filtration~~ filtering is conducted at a transmembrane pressure of from about 0.1 psi to about 7 psi.

16. The process of claim 11, wherein the ~~primary filtration~~ filtering further comprises back pulsing with a back pulse volume and a retentate back pressure.

17. The process of claim 16, wherein the back pulsing is periodic.

18. The process of claim 17, wherein the back pulsing step occurs from about every 0.5 to about every 10 minutes.

19. The process of claim 18, wherein the back pulsing step occurs from about every 1 to about every 5 minutes.

--Claim 20. The process of claim 16, wherein the back pulse volume is from about 0.01% to about 5% of initial filtration volume.--

--Claim 21. The process of claim 20, wherein the back pulsing volume is from about 0.1% to about 1.0% of initial filtration volume.--

--Claim 22. The process of claim 16, wherein the filtering is conducted at a retentate back pressure of from about 0 psi to about 10 psi.--

--Claim 24. The process of claim 23, wherein the potency adjustment is carried out by secondary filtration.--

--Claim 28. The process of claim 27, wherein a first solvent removal step is characterized by an inert gas flow rate that is less than that of a second step.--

--Claim 29. The process of claim 28, wherein the gas flow rate of the first solvent removal step is from about 20% to about 50% that of the second step.--

--Claim 30. The process of claim 27, wherein a first solvent removal step is characterized by an inert gas flow rate that is greater than that of the second step.--

--Claim 31. The process of claim 30, wherein the gas flow rate of the first solvent removal step is from about 120% to about 400% that of the second step.--

--Claim 32. The process of claim 28, further comprising a third solvent removal step, wherein the gas flow rate of the third solvent removal step is less than that of the second solvent removal step.--

33. The process of claim 1, wherein the first aqueous phase comprises a physiologically active substance, and the multivesicular liposomal particle composition comprises an encapsulated physiologically active substance.

34. The process of claim 33, wherein the physiologically active substance is selected from the group consisting of antianginas, antiarrhythmics, antiasthmatic agents, antibiotics, antidiabetics, antifungals, antihistamines, antihypertensives, antiparasitics, antineoplastics, antitumor drugs, antivirals, cardiac glycosides, hormones, immunomodulators, monoclonal antibodies, neurotransmitters, nucleic acids, proteins, radio contrast agents, radionuclides, sedatives, analgesics, steroids, tranquilizers, vaccines, vasopressors, anesthetics, peptides, prodrugs and pharmaceutically acceptable salts of the same.

35. The process of claim 34, wherein the physiologically active substance is selected from cytarabine, insulin, paclitaxel, 5-fluorouracil, floxuridine, morphine, hydromorphine, dexamethasone, methotrexate, bleomycin, vincristine, vinblastine, IgF-1, bupivacaine and amikacin.

claim 36-48 cancelled

--Claim 49. (Currently amended) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase ~~in a mixer with an energy input~~ to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles ~~of pre-determined size relative to energy input~~ of pre-determined, uniform size distribution; ~~and~~

d) ~~filtering~~ adjusting the concentration of the multivesicular liposomal particle composition by cross-flow filtration[[,]] ; and

e) sterilizing the multivesicular liposomal particle composition.

claim 50 cancelled

51. The process of claim 23, wherein the volume of multivesicular liposomal particle composition is pooled and further processed by multiple batch processing.

-- 52 (New) The process of claim 33 wherein the encapsulation efficiency of the physiologically active substance is at least about 67.8%. --

-- 53 (New) The process of claim 1, wherein the mean particle size before cross-flow filtration is within about 1 micron of the mean particle size after cross-flow filtration. --

--Claim 54. A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase in a mixer with a power input to provide a second emulsion, said second emulsion comprising a continuous aqueous phase; and

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined size relative to power input;

wherein power = (linear flow rate through mixer) x (pressure drop across mixer).

Claim 55. The process of claim 54, wherein all steps are carried out under aseptic conditions, wherein all solutions are sterile filtered prior to use, and wherein the multivesicular liposomal particle composition is immediately suitable for administration into humans.

Claim 56. The process of claim 54, wherein the resulting multivesicular liposomal particle composition is sterilized before filling, and wherein the multivesicular liposomal particle composition is immediately suitable for administration into humans.

Claim 57. The process of claim 54, wherein the mixer is a static mixer.

Claim 58. The process of claim 54, wherein the first emulsion and the second aqueous solution are passed through the mixer at a linear velocity of from about 100 cm/min to about 500 cm/min.

Claim 59. The process of claim 54, wherein the volume ratio of the first aqueous phase to the water-immiscible solvent phase is from about 0.33 to about 16.

Claim 60. The process of claim 54, wherein the volume ratio of the first emulsion to the second aqueous phase is from about 0.05 to about 0.5.

Claim 61. The process of claim 54, wherein the solvent removal comprises contacting the second emulsion with an inert gas flow.

Claim 62. The process of claim 54 further comprising filtering the multivesicular liposomal particle composition by cross-flow filtration. --

--Claim 63. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) pre-sterilizing all composition ingredients;

b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

c) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution; and

e) exchanging buffer in the multivesicular liposomal particle composition by cross-flow filtration,

wherein all steps are carried out under aseptic conditions.

Claim 64. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) pre-sterilizing all composition ingredients;

b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

c) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution; and

e) removing unencapsulated drug in the multivesicular liposomal particle composition by cross-flow filtration,

wherein all steps are carried out under aseptic conditions.

Claim 65. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution;

d) exchanging buffer in the multivesicular liposomal particle composition by cross-flow filtration; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 66. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution;

d) removing unencapsulated drug in the multivesicular liposomal particle composition by cross-flow filtration; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 67. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) pre-sterilizing all composition ingredients;

b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

c) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution; and

e) filtering the multivesicular liposomal particle composition by cross-flow filtration to adjust the concentration,

wherein all steps are carried out under aseptic conditions.

Claim 68. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution;

d) filtering the multivesicular liposomal particle composition by cross-flow filtration to adjust concentration; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 69. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) pre-sterilizing all composition ingredients;

b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

c) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution; and

e) filtering the multivesicular liposomal particle composition by cross-flow filtration to exchange buffer therein,

wherein all steps are carried out under aseptic conditions.

Claim 70. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) pre-sterilizing all composition ingredients;

b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

c) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution; and

e) filtering the multivesicular liposomal particle composition by cross-flow filtration to remover unencapsulated drug therein,

wherein all steps are carried out under aseptic conditions.

Claim 71. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution;

d) filtering the multivesicular liposomal particle composition by cross-flow filtration to exchange buffer; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 72. (New) A process for preparing a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution;

d) filtering the multivesicular liposomal particle composition by cross-flow filtration to remove unencapsulated drug; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 73. (New) The process of any of claims 1, 63, 64, 67, 69 or 70 wherein pre-sterilization of all composition ingredients is conducted by filtration through a filter having pores at least as small as 0.22 μm.

Claim 74. (New) A method for increasing the yield of a process for making a multivesicular liposomal composition, the method comprising:

a) pre-sterilizing all composition ingredients;

b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

c) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution; and

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution; and

e) removing unencapsulated drug in the multivesicular liposomal particle composition by cross-flow filtration,

wherein all steps are carried out under aseptic conditions.

Claim 77. (New) A method for increasing the yield of a process for making a multivesicular liposomal composition, the method comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution;

d) adjusting the concentration of the multivesicular liposomal particle composition by cross-flow filtration; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 78. (New) A method for increasing the yield of a process for making a multivesicular liposomal composition, the method comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of multivesicular liposomal particles of pre-determined, uniform size distribution;

d) exchanging buffer in the multivesicular liposomal particle composition by cross-flow filtration; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 79. (New) A method for increasing the yield of a process for making a multivesicular liposomal composition, the method comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution;

d) removing unencapsulated drug in the multivesicular liposomal particle composition by cross-flow filtration; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 80. (New) A method for increasing the yield of a process for making a multivesicular liposomal particle composition, the process comprising:

a) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

b) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

c) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution;

d) filtering the multivesicular liposomal particle composition by cross-flow filtration to perform at least one process selected from the group consisting of concentration adjustment, buffer exchange and removal of unencapsulated drug; and

e) sterilizing the multivesicular liposomal particle composition,

wherein all steps are carried out under aseptic conditions.

Claim 81. (New) A method for increasing the yield of a process for making a multivesicular liposomal particle composition, the process comprising:

a) pre-sterilizing all composition ingredients;

b) providing a first emulsion by mixing a first aqueous phase and a volatile water-immiscible solvent phase, said solvent phase comprising at least one amphipathic lipid and at least one neutral lipid;

c) mixing and emulsifying said first emulsion and a second aqueous phase to provide a second emulsion, said second emulsion comprising a continuous aqueous phase;

d) removing the volatile water-immiscible solvent from the second emulsion to form a composition of drug-containing multivesicular liposomal particles of pre-determined, uniform size distribution; and

e) filtering the multivesicular liposomal particle composition by cross-flow filtration to perform at least one process selected from the group consisting of concentration adjustment, buffer exchange and removal of unencapsulated drug,

wherein all steps are carried out under aseptic conditions.

Claim 82. (New) A product produced in accordance with the process of claim 1.

Claim 83. (New) A product produced in accordance with the process of claim 49.

Claim 84. (New) In a process for preparing a multivesicular liposomal composition comprising a sterilization step, preparation of first and second emulsion steps, and a solvent removal step, the improvement comprising the further step of cross-flow filtration to adjust concentration.

Claim 85. (New) In a process for preparing a multivesicular liposomal composition comprising a sterilization step, preparation of first and second emulsion steps, and a solvent removal step, the improvement comprising the further step of cross-flow filtration to perform buffer exchange.

Claim 86. (New) In a process for preparing a drug-containing multivesicular liposomal composition comprising a sterilization step, preparation of first and second emulsion steps, and a solvent removal step, the improvement comprising the further step of cross-flow filtration to remove unencapsulated drug.

Claim 87. (New) In a process for preparing a multivesicular liposomal composition comprising a sterilization step, preparation of first and second emulsion steps, and a solvent removal step, the improvement comprising the further step of adjusting concentration by cross-flow filtration.

Claim 88. (New) In a process for preparing a multivesicular liposomal composition comprising a sterilization step, preparation of first and second emulsion steps, and a solvent removal step, the improvement comprising the further step of performing buffer exchange by cross-flow filtration.

Claim 89. (New) In a process for preparing a drug-containing multivesicular liposomal composition comprising a sterilization step, preparation of first and second emulsion steps, and a solvent removal step, the improvement comprising the further step of removing unencapsulated drug by cross-flow filtration.--